Prognostic factors for survival after meningioma resection; a consecutive series of 1469 meningioma patients

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Forord

Studentoppgaven ” Prognostic factors for survival after meningioma resection; a consecutive series of 1469 meningioma patients” er basert på et stort datamateriale innhentet fra Oslo Universitetssykehus (Rikshospitalet og Ullevål Universitetssykehus). Arbeidet har foregått i tidsrommet våren 2010 - høsten 2012. Vi har vært fire studenter involvert i prosjektet, der hver av oss har skrevet egne oppgaver.

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KEY WORDS:

Meningioma - Craniotomy – Neoplasm – Intracranial tumor – Complications – Surgical mortality – Survival

ABSTRACT

Aim: The aim of the present study was to explore prognostic factors for survival in a large series of surgically treated meningiomas.

Material & methods: Retrospective study of 1469 consecutive craniotomies for histological verified intracranial meningiomas at the Oslo University Hospital in the time period 1990-2010.

Results: The median age at surgery was 58 years (range 10-92 years), with a male-to-female ratio of 1:2.36. Follow-up was 100%. Median observation time was 6.9 years (range 0.0-20.9). The surgical mortality was 1.9%, 2.7% were reoperated for hematoma and 2.6% reoperated for deep infection. The 1-, 5- and 10-years OS after surgery was 96%, 87% and 76%, respectively. Increasing age, male sex, WHO grade II/III and residual tumor after surgery were identified as significant negative prognostic factors. In this series, tumor location was not associated with OS.

Conclusions: The 1-, 5- and 10-years OS after surgery was 96%, 87% and 76%, respectively. Increasing age, male sex, WHO grade II/III and residual tumor after surgery were identified as negative prognostic factors. In this series, tumor location was not associated with OS. In our opinion the goal of meningioma surgery should always be complete resection.

INTRODUCTION

The incidence of primary intracranial tumors in Norway is 24.2 per 100,000 person-years and meningiomas account for 31% of these tumors, with an incidence of 7.5 per 100,000 person-years.[1] There has been an increase in new cases of meningiomas during the last decades.[2] Females have a well-known increased risk of developing meningiomas, and meningiomas show a marked and quite linear increase in incidence with advancing age.[3, 4]

According to WHO meningiomas are classified into three histological grades with increasing malignancy. Meningiomas are further subdivided according to dural attachment/origin; e.g. convexity-, parasagittal-, falx-, lateral sphenoid wing, supratentorial skull base, posterior fossa- and intraventricular meningiomas.[5]

The main treatment strategy for meningiomas is surgical resection of symptomatic meningiomas. The aim is complete resection including resection of dural attachment in order to achieve Simpson resection grade I.[6] Subtotally resected tumors are either observed or the residual tumor is subjected to stereotactic radiosurgery (SRS). Fractionated radiotherapy of the tumor region after surgical resection is considered in cases of WHO grade II and III tumors. The following variables have in previous studies been identified as prognostic factors for survival of meningioma patients after surgical resection: age, gender, preoperative Karnofsky performance status, tumor location (dural attachment), WHO grade, Simpson resection grade, high MIB-1 index, loss of chromosome 1-p and expression of vascular endothelial growth factor (VEGF).[6-8, 10-21, 23-25, 28-35, 40, 44-57]

The aim of the present study was to explore the validity of some of the above-mentioned prognostic factors for survival in our large consecutive series of surgically treated meningiomas (n = 1469).

MATERIALS AND METHODS

PATIENTS

A total of 1469 consecutive craniotomies for histological verified intracranial meningiomas at the Oslo University Hospital in the time period 1990-2010 were included in this study (Table 1). Reviewing operative protocols identified patients treated in 1990 – 2002, while patients operated after 2002 were identified from our prospectively collected tumor database.

Data was obtained from patients' medical records from Oslo University Hospital, including clinic records of pre- and postoperative visits, operative notes, discharge summaries, pathology reports, and radiological data. The preoperative, post-contrast imaging studies were reviewed to confirm tumor location/dural attachment. In each case, the extent of resection was graded using the Simpson grading scale (Grade 1. Macroscopically complete removal with excision of dural attachment and abnormal bone, Grade 2. Macroscopically complete with endothermic coagulation of dural attachment, Grade 3. Macroscopically complete without resection or coagulation of dural attachment or of its extradural extensions, Grade 4. Subtotal resection, and Grade 5. Simple decompression/biopsy).[6] This information was obtained from the operative notes and postoperative CT/MR.

The following variables were registered: gender, age, presenting symptoms (seizures, increased intracranial pressure, neurological deficits), tumor location (convexity, parasagittal, falx, lateral sphenoid wing, supratentorial skull base, posterior fossa and intraventricular), Simpson resection grade[6], re-operation for postoperative hematoma (extradural, subdural, intracerebral), reoperation for postoperative infection (extradural, subdural, intracerebral or infected bone flap), WHO histological grade. The criteria for meningioma grading have changed over the last 20 years. From 1990 to 2001, the tumors were classified as benign, atypical or anaplastic. The present WHO-grading system for meningioma was implemented in 2001, which divides the tumors into grade I, II and III. For this study, we reclassified the tumors operated before 2001 to the present WHO classification; benign = WHO grade I, atypical = WHO grade II and anaplastic = WHO grade III.

The endpoint of the study was overall survival, defined as time from resection to death. Vital status (dead or alive) and time of death was obtained from the Norwegian Population Registry (Folkeregisteret) January 27th, 2011. The surgical mortality was defined as death of any cause within 30 days of surgery.

ETHICS

The Data Protection Official at Oslo University Hospital approved the study.

STATISTICS

SPSS/PASWStatistics 18.0.3 for Windows (SPSS Inc.) and R v 2.15 were used for statistical analyses. Summaries of the data are shown using counts and percentages. For the survival analysis, we first generated a plot using the Kaplan-Meier estimator. The general population curve was obtained by matching each meningioma patient on sex, age within 10 years and cohort on lifetables from Statistics Norway (http://www.ssb.no/). Uni- and multivariate Cox regression modeling was used for further survival analysis after ascertaining that the assumptions of proportional hazard were fulfilled. Significance was defined as $p < 0.05$.

RESULTS

Patient characteristics

The median age at surgery was 58 years (range 10-92 years), with a male-to-female ratio of 1:2.36. Follow-up was 100%. Median observation time was 6.9 years (range 0.0-20.9). Patient characteristics are given in Table 1.

Quality parameters for surgery

28 patients died within 30 days of surgery, yielding a surgical mortality rate of 1.9%. The surgical mortality decreased from 3.5% in 1990-1994 to 1.1% in 2005-2010 (Table 2). The rate of postoperative hematomas requiring surgical evacuation was 2.7% (n=40). The median time to reoperation was 2 days (range 0-232)**.** 38 patients (2.6%) were reoperated due to deep infection after a median of 42 days (range 2-2324)**.** The rates of reoperation for postoperative hematoma or local infection showed no significant change over time (Table 2).

Overall survival (OS)

1-, 5- and 10-year overall survival (OS) after surgery was 95.5%, 86.5% and 75.9%, respectively. Figure 1 displays the Kaplan-Meier curves stratified by WHO-grade. A Kaplan-Meier curve matched by age, sex and cohort to the meningioma patients is also shown for reference. There is a significantly worse survival for patients harboring a meningioma, irrespective of WHO-grade, compared to the general population ($p<0.05$). Furthermore, WHO II and III grade portends a worse prognosis than WHO grade I.

A univariate- and multivariate regression analysis of variables with possible association to OS of meningioma patients after tumor resection is presented in Table 3. The following parameters were identified as negative prognostic factors with respect to OS: Increasing age, male sex, WHO grade II/III tumors and residual tumor after surgery. Tumor location was in this material not associated with survival.

WHO grade II/III tumors were significantly more frequent in males than females (Table 4).

DISCUSSION

In this series of 1469 consecutive patients treated with craniotomy and surgical resection of meningioma the surgical mortality was 1.9%, 2.7% were reoperated for hematoma and 2.6% reoperated for deep infection. The 1-, 5- and 10-years OS after surgery was 96%, 87% and 76%, respectively. Increasing age, male sex, WHO grade II/III and residual tumor after surgery were identified as negative prognostic factors. In this series, tumor location was not associated with OS. To the best of our knowledge, this is one of the largest single-institution, clinically based surgical series of intracranial meningioma published.

Quality of surgery

Quality of surgery is one of many factors that have an impact on OS. Thus, when addressing risk factors for OS the quality of surgery should also be discussed. Surgical mortality, the rate of postoperative hematoma, the rate of deep postoperative infection and neurological deterioration after surgery are all well accepted indicators for quality of surgery. Three of the four mentioned quality indicators were included in this study. Unfortunately, the retrospective chart review gave no reliable information regarding neurological deterioration.

Surgical mortality

The surgical mortality after craniotomy for tumors is reported to be between 0 – 10.8%.[9-16] Our surgical mortality of 1.9% is in the lower part of this specter. The decrease in surgical mortality over time is most likely multifactorial; e.g. better preoperative imaging, improvements in neuro-anesthesiology and improvements in surgical technique. This positive time trend with respect to surgical mortality has also been reported by others.[14, 15]

Reoperation for postoperative hematoma

The rate for postoperative hematoma after craniotomy for tumor has been reported to be between 0.6% and 4%.[9, 10, 17-25] Palmer et al identified meningioma as a risk factor for postoperative hematoma compared to intrinsic tumors.[17] However, in a large series from our hospital studying complications after craniotomy there was no difference in hematoma rates after surgery for intrinsic or extrinsic intracranial

tumors.[9] Our hematoma rate of 2.7% is in the middle of the range reported for meningiomas. Postoperative hematoma is a contributor to surgical mortality and morbidity.[9]

Reoperation for deep infection

2.6% of the patients in our series were complicated with a surgical site infection (extradural, subdural, intracerebral or infected bone flap) that required reoperation. The rate of reoperation for deep infection after craniotomy for tumor is reported to be between 0.6% and 6.6% (reviewed in Lassen et al).[9] Reviewing only meningiomas, the rate ranges from 0.5% to 6.2%.[10, 19, 20, 22, 24, 26, 27] Postoperative infection causes prolonged hospitalization and increased costs. However, the long-term result with regard to survival and neurological outcome is less affected than after postoperative hematoma.[10]

Overall survival and factors associated with overall survival

The overall survival rates following craniotomy for meningioma has been reported to be 82 – 91% at 1-year, 55 – 83% at 5-years and 33 – 77% at 10-years.[6, 14, 28-30] In our series the 1-, 5- and 10-year survival rates were 96%, 87% and 76%, respectively.

Age

We found age to be a negative prognostic factor for OS. This has been widely reported in previous studies.[14, 15, 21, 23, 28, 31-33] Mortality not related to the meningioma itself is considerable in the elderly patients. Thus, the OS of meningioma patients should be compared with the expected OS of a general population comparable to the patients. Doing this, we found the OS following craniotomy for any meningioma to be significantly worse than for the matched general Norwegian population, both for WHO grade I and WHO grade II/III patients. Others have reported insignificant differences in survival between patients with WHO grade I meningioma and the matched general population.[34] Although higher age is associated with reduced OS, it should not alone be used as a selection criterion, as quality of life following meningioma surgery is improved in the majority of elderly patients.[24, 25, 35]

Sex

It is well known that women develop meningiomas to a greater extent than men. The mechanisms for this are not entirely understood, but endocrinological influence is believed to play an important role.[36-38] Nonetheless, overall survival was in this series found to be worse for men. This is in accordance with previous studies.[15, 28, 39] Contrary to these findings, Duntze et al reported female sex as a negative prognostic factor.[33] The fact that their study included only 36 patients and excluded WHO grade I is of relevance. A possible explanation for the poorer OS in men is the greater frequency of WHO grade II/III tumors in men compared to women. This has also been commented in previous series.[14, 40-44] Interestingly, Whittle et al showed that progesterone activity correlates inversely with malignancy in meningiomas[45], the opposite of what is believed for benign meningiomas.

Simpson resection grade

Many previous publications have addressed the relevance of radical tumor resection and its association to tumor recurrence.[6, 18, 46-48] The relation to OS has not been discussed to the same extent. Chan and Thompson found a difference in 3.3 years in average survival time between total excision and partial removal of tumor.[10] A study published by Sughrue et al in 2010 indicated that differences in outcome between Simpson grade 1 and 2 were negligible, although only reviewing WHO grade I meningiomas.[49] In our series, subtotal resection (Simpson grade 4/5) was associated with reduced OS. In our opinion the goal of meningioma surgery is Simpson resection grade 1-3, depending on tumor location.

WHO grade

WHO grade was as a significant prognostic factor with respect to OS in our material, as in previous series, with poorer survival for WHO grade II and III.[10, 14, 15, 23, 29, 32, 50, 51] In our series, the 5-year survival rate for WHO grade I, II and III were 88%, 75% and 66%, respectively. The range of reported survival rates for the different WHO grades are wide, especially for grade III. The 5-year survival rate for WHO grade I tumors is reported to be 75-93%, for WHO grade II 50-80% and for WHO grade III 8 – 62%.[29, 31-34, 40, 44, 52]

Tumor location

No statistical difference in survival for the various tumor locations was found in our study. Published series has so far given no general consensus regarding the impact of tumor location with respect to survival.[13, 15, 16, 19, 51, 53]

Other prognostic factors

There are other well-known prognostic factors that where not studied in our series. The following factors have in previous studies been associated with reduced OS: impaired preoperative neurological function, lack of calcification in the tumor, a high MIB-1 index, loss of chromosome 1-p and expression of vascular endothelial growth factor (VEGF).[10, 51, 54-57]

Strengths of the study

The strengths of this study lie in the setting, design and follow-up. The data were restricted to one health centre only (Oslo University Hospital), thereby reducing the possible confounding effect of differences in the access to health care services between health centers. Thus, we have avoided the selection bias inherently present in large multi-center studies. The two-neurosurgical units performing these surgeries are within a geographically well-defined area. As the study includes all craniotomies performed for histologically verifiable meningiomas, there is no selection bias. With respect to data quality, we only used end points that are easily verifiable (i.e. mortality, reoperation for hematomas and reoperations for infections).

Limitation of the study

The main limitation of the study is the retrospective design.

CONCLUSIONS

The 1-, 5- and 10-years OS after surgery was 96%, 87% and 76%, respectively. Increasing age, male sex, WHO grade II/III and residual tumor after surgery were identified as negative prognostic factors. In this series, tumor location was not associated with OS. In our opinion the goal of meningioma surgery should always be complete resection.

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Figure 1. Kaplan-Meier curves for OS stratified by WHO-grade. A Kaplan-Meier curve matched by age, sex and cohort to the meningioma patients is also shown for reference (= general population).

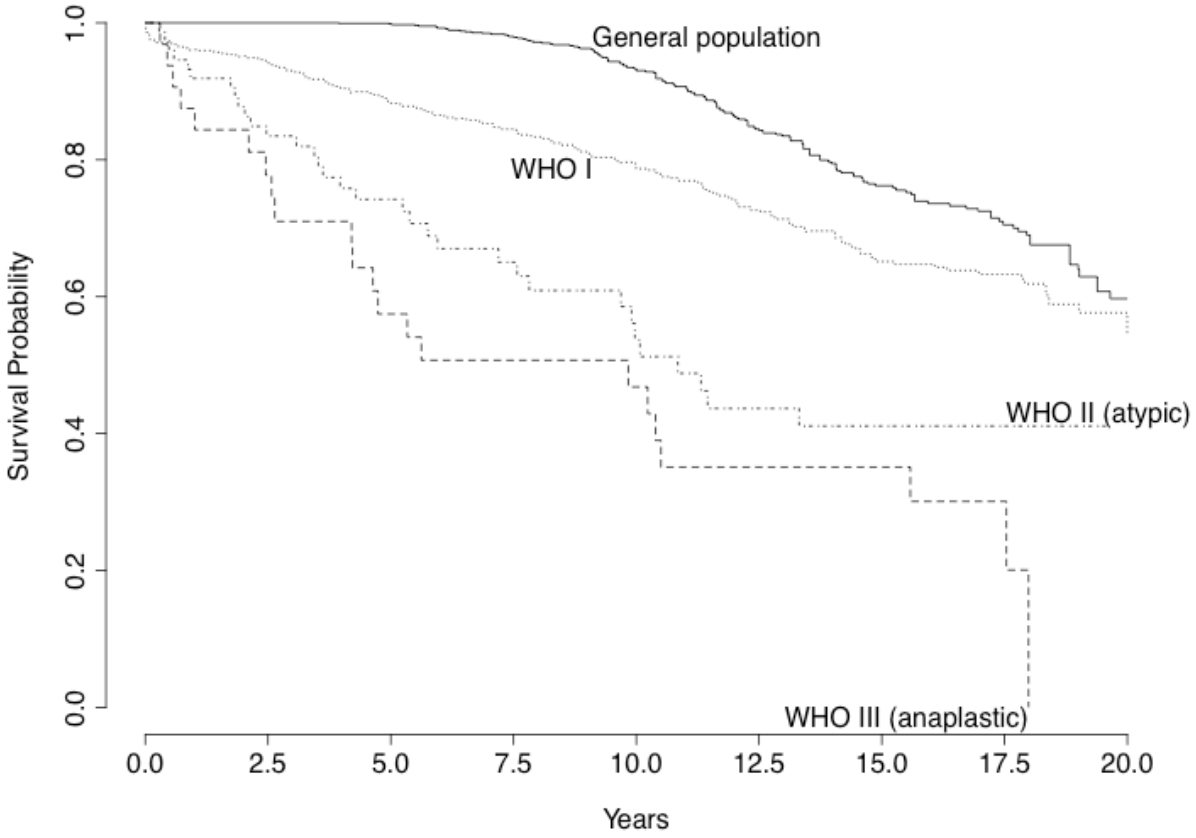

Table 1. Patient characteristics

		N (%)
All		1469 (100)
Gender	Females	1033 (70.3)
	Males	436 (29.7)
Age	15 – 29	17 (1.2)
	30 – 39	126 (8.6)
	40 – 49	256 (17.4)
	50 –59	396 (27.0)
	60 – 69	352 (24.0)
	70 –79	273 (18.6)
	80+	49 (3.3)
Signs/symptoms at presentation		1389 (94.6)
Tumor location	Convexity	391 (26.6)
	Parasagittal	201 (13.7)
	Falx	164 (11.1)
	Lat sphenoid wing	94 (6.4)
	Skullbase ST[1]	398 (27.1)
	Posterior fossa	198 (13.5)
	Intraventricular	23 (1.6)
Surgical approach	Supratentorial	1271 (86.5)
	Infratentorial	198 (13.5)
Simpson resection grade[2]	1	575 (39.1)
	2	504 (34.2)
	3	79 (5.4)
	4	302 (20.6)
	5	8 (0.5)
WHO grade	I	1359 (92.5)
	II	78 (5.3)
	III	32 (2.2)

[1] Supratentorial

[2] Information of radicality missing for two patients.

Table 2. Time trend of surgical mortality,

Time period	Total number of patients	Surgical mortality (%)	Reop for Hematoma (%)	Reop for deep infection (%)
1990-1994	260	3.5	1.5	1.2
1995-1999	280	2.5	3.9	2.1
2000-2004	381	1.6	2.6	3.1
2005-2010	548	1.1	2.7	3.1
TOTAL	1469	1.9	2.7	2.6

Table 3. Univariate and multivariate Cox regression analyses of factors associated with overall survival

Variable	Univariate analysis		Multivariate analysis	
	[1]HR	95% conf.int	HR	95% conf.int
Age	1.093	(1.081, 1.105)***	1.095	(1.083, 1.107)***
Sex				
Male		Ref		
Female	0.537	(0.432, 0.669)***	0.659	(0.526, 0.827)***
Dural attachment				
Convexity		Ref		
Posterior Fossa	0.965	(0.673, 1.386)	0.976	(0.626, 1.524)
Falx	0.909	(0.607, 1.362)	0.994	(0.639, 1.545)
Lateral sphenoid wing	0.924	(0.556, 1.534)	1.161	(0.672, 2.007)
Skullbase supratentorial	1.038	(0.776, 1.389)	1.157	(0.794, 1.685)
Parasagittal	1.198	(0.849, 1.691)	0.994	(0.674, 1.466)
Intraventricular	0.748	(0.237, 2.366)	1.512	(0.474, 4.828)
Histological grade				
WHO I		Ref		
WHO II (atypic)	2.313	(1.610,3.322)***	2.200	(1.507,3.212)***
WHO III (anaplastic)	3.412	(2.207, 5.275)***	3.074	(1.956, 4.832)***
Simpson resection grade				
1		Ref		
2	0.940	(0.714, 1.236)	0.982	(0.701, 1.376)
3	1.062	(0.636, 1.775)	0.928	(0.542, 1.590)
4	2.062	(1.571, 2.707)***	2.358	(1.660, 3.348)***
5	2.189	(0.694, 6.900)	1.700	(0.416, 6.943)

[1]HR = Hazard Ratio

* p<0.05, ** p<0.01, *** p<0.001

Table 4. Gender and WHO grade.

	Male %	Female %
WHO I	89	94
WHO II	7.3	4.5
WHO III	3.7	1.5
TOTAL	100	100